93. (Amended) The method of claim 88, wherein the ATP-binding cassette (ABC)-encoding nucleic acid encodes ABCA1, ABCA2, ABCA3, ABCA4, ABCA5, ABCA6, ABCA7, ABCA8, ABCA9, ABCA10, ABCA11, ABCA12, ABCA13, ABCA14, ABCB1, ABCB2, ABCB3, ABCB4, ABCB5, ABCB6, ABCB7, ABCB8, ABCB9, ABCB10, ABCB1, ABCC1, ABCC2, ABCC3, ABCC4, ABCC5, ABCC6, ABCC7, ABCC8, ABCC9, ABCC10, ABCC11, ABCC12, ABCC13, ABCD1, ABCD2, ABCD3, ABCD4, ABCE1, ABCF1, ABCF2, ABCF3, ABCG1, ABCG2, ABCG4, ABCG5, or ABCG8.

94. (Amended) The method of claim 93, wherein the ATP-binding cassette (ABC)-encoding nucleic acid encodes BCRP1.

III. RESPONSE TO OFFICE ACTION

A. Objections to the Specification

The specification is objected to because the specification contains sequences (primers) at page 113 that are not listed in the sequence listing or CRF and are not represented by a sequence identifier (SEQ ID NO:). Applicants have provided herein a substitute sequence listing which includes SEQ ID Nos for the appropriate primers at page 113.

B. Objections to the claims

Claims 80 and 81 are objected to because of the sequence identifiers are incorrect. Applicants have amended claims 80 and 81 to recite "SEQ ID NO:" instead of "SEQ. ID. NO."

C. Status of the Claims

Due to a Restriction Requirement dated October 10, 2001, Applicants elected Group IV, claims 77-84 and 88-97 drawn to a method for evaluating the toxicity of flavopiridol in a patient. In an Restriction Requirement dated June 4, 2002, Applicants were subjected to further

restrictions of Group IV, claims 77-84 and 88-97. In response to the Restriction Requirement dated June 4, 2002, Applicants elected with traverse to prosecute the ABC-encoding nucleic acid that encodes ABCG2.

Claims 77-84 and 88-97 were pending prior to the Office Action dated August 28, 2002. Claims 77, 79, 80-84, 88, and 90-94 have been amended herein in Appendix A. Support for the amendments may be found in the claims and specification as originally filed. No new matter has been added.

Therefore, the claims pending in the present application are claims 77-84 and 88-97, a copy of which is attached hereto for the Examiner's convenience in Appendix B.

D. Claim Rejections under 35 U.S.C. §112, first paragraph

1. Claims 77-84 and 88-94 are enabled

Claims 77-84 and 88-94 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. The Action states the claimed invention is drawn to a method of evaluating the risk of flavopiridol-induced toxicity in a patient comprising evaluating a UGT1A9-encoding nucleic acid or a ABC-encoding nucleic acid of the patient for a polymorphism. The Action contends that the specification however fails to identify what the SCA2-SNP is or how the SCA2 is related to the method of evaluating the risk of flavopiridol- induced toxicity. The Action also contends that the specification fails to identify or disclose any SNP or polymorphism associated with flavopiridol- induced toxicity.

The Action also contends that the specification does not define any polymorphisms of the UGT1A9-encoding nucleic acid or the ABC-encoding nucleic acid. The Action concludes that the claimed invention provides insufficient guidance and direction and lacks proper working examples for one skilled in the art to make and use the claimed invention without undue experimentation.

Applicants traverse the rejection and provide the following evidence that the Applicants' invention is enabled. The Applicants state that the enablement requirement is met by describing any mode of enablement of the invention. Throughout the specification Applicants have described the UGT1A9 nucleic acids, for example, see pages 75 to 81 of the specification. Applicants have also provided in the sequence listing the nucleic acid sequences of the claimed invention. At pages 24-27 Applicants provide detail description of flavopiridol, correlation of glucuronidation and flavopiridol toxicity, the role of ATP-binding cassette (ABC) proteins in regulating flavopiridol toxicity, genetic polymorphism of flavopiridol, and the involvement of UDP-glucuronosyltransferase (UGT) variants in polymorphism of flavopiridol. On pages 73-74 Applicants have provided various ABC proteins along with their respective GenBank Accession numbers. At pages 105-117 Applicants have provided more than adequate written description of assays and screening methods for detecting polymorphisms. In the Examples at pages 118-129, Applicants have provides more than adequate description regarding assay of flavopiridol and FLAVO glucuronidation, screening polymorphisms of UGT for FLAVO activity, and pharmacogenetic screening and polymorphism analysis to detect FLAVO drug toxicity. Figure 7 shows the contribution of UGT isoforms to the formation of FLAVO-G.

The Applicants state that the Examiner has not shown that the specification is not enabled. The Applicants further state that the initial burden of proof to show reasons for

doubting enablement rests with the Examiner. Only after the Examiner meets his or her initial burden does the burden shift to the applicant to provide suitable proof of enablement. The Applicants thus cite *In re Wright*, 999 F.2d 1557, 1561-62, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993):

> "When rejecting a claim under the enablement requirement of section 112, the PTO bears an initial burden of setting forth a reasonable explanation as to why it believes that the scope of protection provided by that claim is not adequately enabled by the description of the invention provided in the specification of the application; this includes, of course, providing sufficient reasons for doubting any assertions in the specification as to the scope of enablement. If the PTO meets this burden, the burden then shifts to the applicant to provide suitable proofs indicating that the specification is indeed enabling.".

The Applicants reiterate that the enablement requirement is met by describing any mode of enablement of the invention. Thus, the Applicants have provided evidence that makes moot the rejection of the claims as lacking enablement from the specification, figures and the sequence listing as described above.

In light of the foregoing arguments, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 77-84 and 88-94 as lacking enablement under U.S.C. 35 §112, first paragraph.

2. Claims 77-84 and 88-94 meet the Written Description requirement.

Claims 77-84 and 88-94 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The Action contends the disclosure of evaluating a UGT1A9-encoding nucleic acid or ABC-encoding nucleic acid for a polymorphism encompasses a large number of nucleic acid species not described or disclosed anywhere in the specification.

The Action further contends that a representative number of species for each genus must be disclosed to meet the written description requirement of 112, first paragraph. The Action further states that absent a written description disclosing a representative number of species as claimed in claims 77-84 and 88-94 of the specification fails to show that Applicants were, in fact, "in possession of the claimed invention" at the time the application for patent was filed.

Applicants traverse the rejection and provide the similar arguments as stated above for enablement. Applicants state "Possession may be shown in a variety of ways including . . . by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention. *See, e.g., Pfaff v. Wells Electronics, Inc.*, 525 U.S. 55, 68, 119 S.Ct. 304, 312, 48 USPQ2d 1641, 1647 (1998); *Eli Lilly*, 119 F.3d at 1568, 43 USPQ2d at 1406; *Amgen, Inc. v. Chugai Pharmaceutical*, 927 F.2d 1200, 1206, 18 USPQ2d 1016, 1021 (Fed. Cir. 1991); MPEP 2163."

Applicants have provided an adequate written description to allow one of skill in the art to practice the claimed invention. Throughout the specification Applicants have described the UGT1A9 nucleic acids, for example, see pages 75 to 81 of the specification. Applicants have also provided in the sequence listing the nucleic acid sequences of the claimed invention. At pages 24-27 Applicants provide detail description of flavopiridol, correlation of glucuronidation and flavopiridol toxicity, the role of ATP-binding cassette (ABC) proteins in regulating flavopiridol toxicity, genetic polymorphism of flavopiridol, and the involvement of UDP-glucuronosyltransferase (UGT) variants in polymorphism of flavopiridol. On pages 73-74 Applicants have provided various ABC proteins along with their respective GenBank Accession numbers. At pages 105-117 Applicants provide more than adequate written description of assays and screening methods for detecting polymorphisms. In the Examples at pages 118-129,

Applicants have provides more than adequate description regarding assay of flavopiridol and FLAVO glucuronidation, screening polymorphisms of UGT for FLAVO activity, and pharmacogenetic screening and polymorphism analysis to detect FLAVO drug toxicity. Figure 7 shows the contribution of UGT isoforms to the formation of flavopiridol (FLAVO-G).

Thus, the Applicants reiterate that they have provided an adequate description in the disclosure and working examples to show that they had possession of the invention at the time of filing of the application.

In light of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 77-84 and 88-94 as lacking adequate written description under 35 U.S.C. §112 first paragraph.

E. Claim Rejection under 35 U.S.C. §112, second paragraph

1. Claims 77-84 and 88-94 are definite

Claims 77-84 and 88-98 are rejected under 35 U.S.C. §112, second paragraph as being indefinite for failing to particularly point out and distinctly claim the subject matter which the Applicants regard as the invention. The Action contends that claims 77-84 and 88-94 are incomplete and indefinite in claim 77 because it cannot be determined how evaluating a UGT1A9-encoding nucleic acid or ABC-encoding nucleic acid for a polymorphism relates to evaluating the risk of flavopiridol-induced toxicity. The Action further contends that the term "evaluating" is a non-specific activity and therefore is unclear how the claimed method operates to detect the polymorphisms. The Applicants traverse this rejection.

As provided throughout the specification of the application and in the Examples, the variability in flavopiridol to glucuronidation reflects a variability in the genetic differences in the

isozymes which through pharmacogenetic screening identifies individuals predisposed to flavopidirol toxicity.

The specification at page 3, lines 6-10, states that glucuronidation of flavopiridol is the major mechanism of flavopidirol transformation. At page 4, lines 6-7 of the specification states glucuronidation by uridine diphosphate glucuronosyltransferase (UGT) enzymes is a major drug metabolic pathway in humans. At page 8, lines 6-17 applicants provide examples of uridine diphosphate glucuronosyltransferase (UGT) enzymes relevant to the present invention. At page 8 of the specification, Applicants disclose that biliary transport proteins that function to transport flavopidirol are members of the ABC protein family. The paragraphs spanning pages 14-15 of the specification provides examples of ABC family members. Pages 24-27 of the specification disclose that: 1) flavopiridol is transformed to glucuronide which appears to be a polymorphic event; 2) variability in glucuronidation of flavopiridol is mainly responsible for differential accumulation of flavopiridol in patients; 3) the presence of genetic polymorphism of flavopiridol glucuronidation in patients is indicated; 4) that these genetic polymorphisms play a critical role in drug-related toxicity; 5) variants of UGT play a role in the polymorphic metabolism of flavopiridol; 6) and the role of the ABC family of proteins in the biliary transport of flavopiridol as regulators of flavopiridol toxicity. As is further disclosed throughout the specification and the claims, the present invention looks at UGT and ABC and polymorphisms thereof to assay, evaluate, detect or identify the role of these proteins in dictating flavopiridol toxicity to a patient.

Applicants further argue that the term "evaluating" is a specific activity and makes clear how the claimed method operates to detect polymorphisms. As stated above for the argument on indefiniteness, the specification provides a description of the claimed invention so that it would be clear to one of skill in the art what "evaluate" the risk of flavopiridol-induced toxicity means.

Applicants further point out that given the detailed disclosure of the invention, one of ordinary skill in the art would know how to practice the invention. Applicants further state that one of ordinary skill would know that the meaning of the term "evaluate" or inflections thereof, is defined as: to judge or calculate the quality, importance, amount or value of (something); to ascertain or fix the value or worth of; to examine and judge carefully; appraise; to determine the significance, worth, or condition of usually by careful appraisal and study; assess; or assay. (See Cambridge International Dictionary of English; Merriam Webster's Collegiate® Dictionary, 10th Edition; the American Heritage® Dictionary of the English Language; Webster's II New Riverside University Dictionary, 1995; Webster's New Twentieth Century Dictionary, 2nd Edition, 1983, Appendix C).

Thus, in light of the disclosure, it would be more than obvious to one of skill in the art how to practice the claimed invention and that the term "evaluate" is not a non-specific activity. Applicants further state that one of skill in the art would know what subject matter the claims encompass and that the claims as written make clear the subject matter.

The Action further contends that claims 77-84 and 88-94 are indefinite for the abbreviations of "UGT1A9", "ABC", "ABCG2" and BCRP1 because the abbreviations often have more than one meaning in the art. Applicants traverse this rejection but have amended the claims accordingly by inserting the full name of the abbreviation into the claims.

Thus, in light of the foregoing, the Applicants respectfully request that the Examiner reconsider and withdraw the rejection of claims 77-84 and 88-94 for being indefinite under 35 U.S.C. §112, second paragraph.